Claim 17, line 2, delete "8 or".

Claim 22, line 1, delete "receptor" and insert --binding-- in place thereof.

Claim 23, line 1, delete "receptor" and insert --binding-- in place thereof.

Claim 23, lines 2-3, delete "or a functional derivative thereof which is capable of binding to TNF,".

Remarks

Claims 1, 8, 15, and 16 have been canceled. Claims 2-7, 9-14, 17, 18, 22, and 23 are pending in the present application. Claims 2, 7, 9, 13, 17, 22, and 23 have been rewritten to more clearly define what the Applicants consider to be their invention. Canceled claims 1, 8, 15, and 16 were directed to the membrane bound TNF receptor protein and DNA sequences, as well as variants and fragments thereof. Applicants now claim particular DNA molecules coding for soluble TNF binding proteins, and processes for preparing recombinant, soluble TNF binding proteins. Support for the process of preparing soluble TNF binding proteins and corresponding DNA molecules may be found at least in Examples 1-12 of the application. No new matter was added by way of these amendments.

In the Office Action mailed August 28, 1992, the Examiner made one objection to the specification and made three rejections. In response thereto, Applicants respectfully submit the following remarks.

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The Objection Under 35 U.S.C. § 112, First Paragraph May Be Properly Withdrawn

The Examiner has objected to the specification under 35 U.S.C. § 112, first paragraph, on the basis that the specification fails to provide an adequate written description of the invention and fails to provide an enabling disclosure. In particular, the Examiner states that the specification does not enable the ability of "variants" of the TNF-binding protein or the TNF receptor. Applicants submit that the present amendments overcome this basis for objection.

Applicants have amended claims 2, 9, 13, and 23 by deleting references to "variant" or to "functional derivative." Moreover, Applicants have canceled claims 1 and 8 which also referred to a "variant." Therefore, the present claims are not directed to "variant" TNF binding proteins or receptors. Thus, the objection to the specification based upon the alleged lack of adequate written description or enablement for variant proteins is now moot.

In light of the amendments and remarks above, Applicants request the Examiner to withdraw the objection to the specification under 35 U.S.C. § 112, first paragraph.

The Rejection Under 35 U.S.C. § 112, First Paragraph, May Be Properly Withdrawn

The Examiner has rejected claims 1-18, 22, and 23 under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Having overcome this basis for objection to the specification, Applicants submit that the rejection to the claims may be properly withdrawn.

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In light of the amendments and remarks above, Applicants request the Examiner to withdraw the rejection to the claims under 35 U.S.C. § 112, first paragraph. Reconsideration of the claims is respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph, May Be Properly Withdrawn

The Examiner has rejected claims 1-18 and 23 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. In particular, the Examiner states that claims 1, 2, 8, 9, 13, and 23 claim undisclosed fragments, degenerate variants, or functional derivatives of the TNF receptor protein. Applicants submit that the present amendments overcome this basis for rejection.

Applicants have canceled claims 1 and 8 and Applicants have amended claims 2, 9, 13, and 23 by deleting references to "variant, " to "functional derivative," or to "fragments." Applicants have not cancelled the term "or degenerate variant" thereof. Applicants submit that this term is well known to those of ordinary skill in the art. In addition, one of ordinary skill in the art can easily obtain degenerate variants based upon the known degeneracy of the genetic code. Thus, Applicants submit that the rejection to claims 1, 2, 8, 9, 13, and 23 under 35 U.S.C. § 112, second paragraph, has been overcome.

The Examiner also states that claim 7 is vague and indefinite because the claim does not describe precise hybridization conditions. Applicants respectfully traverse this basis for rejection.

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Applicants submit that 35 U.S.C. § 112, second paragraph, does not require a recitation of hybridization conditions in claim 7. According to the Federal Circuit:

> The purpose of this [enablement] provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and knowledge in the art.

Scripps Clinic v. Genentech, Inc., 18 USPQ2d 1001, 1006 (Fed. Cir. 1991). Claim 7 is directed to a nucleic acid which hybridizes with the DNA molecule of claim 2 (i.e., a DNA molecule coding for TNF binding protein) under conditions of low stringency. As noted in Wallach *et al.* (reference AN1), "[p]rocedures for hybridization of nucleic acids are common knowledge . . ." (*see* page 9, line 60 of Wallach *et al.*). In particular, low stringency hybridization techniques are well known to those of ordinary skill in the art (*see*, for example, reference AS8 (submitted herewith), page 890, column 2, third full paragraph, third sentence). A patent need not disclose and preferably omits what is well known to those of ordinary skill in the art. *See Lindemann Machinefabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481,489 (Fed. Cir. 1984). Thus, claim 7 complies with the requirements of 35 U.S.C. § 112, second paragraph.

The Examiner also states that claims 11-16 refer to plasmids which have not been deposited and "are not described in the claims in such a manner that clearly describes what the Applicants view as their invention." Applicants respectfully traverse this basis for rejection.

Claims 11 and 12 are directed to the plasmids pADTNF-BP and pADBTNF-BP, respectively. Applicants submit that the construction of plasmid pADTNF-BP is fully described in Example 13 of the application and that the construction of plasmid pADBTNF-BP is fully described in Example 14 of the application. Moreover, the

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structures of the plasmids are depicted in Figure 7 of the application. Since the specification fully describes the construction of the plasmids, claims 11 and 12 comply with the requirements of 35 U.S.C. § 112, second paragraph.

Applicants note that claims 13 and 14 are not directed to designated plasmids. Moreover, Applicants have canceled claims 15 and 16 without prejudice or disclaimer to the subject matter therein. Thus, the rejection of claims 13-16 under 35 U.S.C. § 112, second paragraph, is now moot.

In light of the amendments and remarks above, Applicants request the Examiner to withdraw the rejection to the claims under 35 U.S.C. § 112, second paragraph. Reconsideration of the claims is respectfully requested.

The Rejection Under 35 U.S.C. § 103 May Be Properly Withdrawn

The Examiner has rejected claims 1-18, 22, and 23 under 35 U.S.C. § 103, as being obvious over Wallach *et al.* (reference AN1). The Examiner states that Wallach *et al.* teach the purification of TNF binding protein from urine and a partial amino acid sequence of the protein. The Examiner's position is that Wallach *et al.* makes the claimed invention obvious because one of ordinary skill in the art can isolate the DNA coding for TNF binding protein based upon the partial amino acid sequence and the isolation method taught by Wallach *et al.* The Examiner concludes that the claimed invention has been taught or is obvious in view of Wallach *et al.*, and the Examiner rejects the pending claims under 35 U.S.C. § 102 or 35 U.S.C. § 103. Applicants respectfully traverse this basis for rejection.

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Applicants submit that Wallach *et al.* do not teach or suggest the claimed invention. Wallach *et al.* disclose the isolation of a TNF binding protein and a partial N-terminal amino acid sequence of the protein. Wallach *et al.* suggest prophetically that the TNF gene could be cloned using antibodies generated against the isolated protein or by using oligonucleotides which could be designed based upon the partial amino acid sequence. Even if one was successful at carrying out these suggestions, then one would obtain the coding sequence for the entire membrane-bound TNF receptor. Applicants' invention is directed to a process of producing the ***soluble*** TNF binding protein, not the membrane-bound TNF receptor. Wallach *et al.* do not teach or suggest the methodology that would be required to modify the TNF receptor coding sequence in order to obtain the soluble TNF binding protein. Thus, Wallach *et al.* do not teach or suggest the claimed invention.

Applicants designed the plasmid pADTNF-BP for the expression of the soluble TNF binding protein (*see* Example 13 of the application). Applicants modified the TNF receptor coding sequences by inserting a translation stop codon after the codon of the C-terminal amino acid of the soluble TNF binding protein (i.e., Asn-172). In addition, Applicants shortened the 5' noncoding region of the TNF receptor cDNA in order to remove the translation start codon of another open reading frame (i.e., bases 72-203). Finally, Applicants inserted particular restriction endonuclease cleavage sites at the 5' and 3' ends of their novel cDNA which codes for soluble TNF binding protein. Applicants stress that Wallach *et al.* do not teach or suggest *any* methodology that would be required to modify the TNF receptor coding sequence in order to obtain the soluble TNF binding protein.

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Moreover, Applicants note that a subsequent application of Wallach *et al.* relates to the expression of the ***soluble*** TNF binding protein (reference AO1, submitted herewith). The fact that over two years have elapsed between the priority date of the first Wallach *et al.* application and the priority date of the second application, and the fact that Wallach *et al.* have deemed the cloning of the TNF binding protein to be worthy of an application for a patent, demonstrate that Applicants' invention is not obvious to one of ordinary skill in the art.

In addition, Applicants note that the Examiner has suggested that the plasmids which code for the TNF binding protein (i.e., pADTNF-BP and pADBTNF-BP) should be deposited to fulfill the requirements of 35 U.S.C. § 112, second paragraph. Apparently, the Examiner does not believe that one of ordinary skill in the art could construct the plasmids without undue experimentation. Thus, Applicants submit that the construction of plasmids coding for the soluble TNF binding protein are not obvious to one of ordinary skill in the art.

The Examiner also states that claims 1-18, 22, and 23 are unpatentable over the combined teachings of Olsson *et al.* (AS5) and Clark *et al.* (Examiner's reference A). The Examiner states that Olsson *et al.* teach the isolation of TNF binding protein from urine and the partial amino acid sequence of the TNF binding protein. The Examiner also states that Olsson *et al.* suggest that TNF binding protein may be a soluble form of the TNF receptor. The Examiner states that Clark *et al.* teach a method of isolating DNA sequences which code for a known protein requiring the identification of cells that produce the protein, isolating mRNA from the cells, synthesizing cDNA from the mRNA, inserting the cDNA into expression vectors, and transforming *E. coli* to express the

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cDNA. The Examiner concludes that it would have been obvious to one of ordinary skill in the art with the knowledge of the partial amino acid sequence and the motivation to isolate the TNF receptor and binding protein, to use the teachings of Clark *et al.* to isolate DNA coding for TNF protein. Applicants respectfully traverse this basis for rejection.

Applicants submit that even if one was successful in cloning TNF nucleic acid sequences, one would obtain the sequence for the *membrane-bound TNF receptor*. The soluble TNF binding protein is derived from the TNF receptor by proteolytic cleavage *in vivo*. As described above, Applicants isolated DNA sequences coding for the TNF receptor protein and then, modified these sequences in order to provide a novel cDNA which codes for the *soluble* TNF binding protein. Neither Olsson *et al.* nor Clark *et al.* teach or suggest a method to isolate nucleic acid sequences coding for the TNF binding protein. Thus, neither Olsson *et al.* nor Clark *et al.* teach or suggest the claimed invention.

In addition, Applicants submit that the rejection under 35 U.S.C. § 103 is based upon an application of the discredited "obvious to try" standard. According to the Federal Circuit, "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 7 USPQ2d 1673, 1681 (Fed.Cir. 1988). An invention is obvious to try where the prior art gives no indication of which parameters are critical or no direction as to which of the many possible choices is likely to be successful. In particular, Clark *et al.* neither state that the TNF binding protein from urine is a proteolytic cleavage product

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nor indicate how to obtain the cDNA coding for the soluble protein. Thus, a finding of obviousness is not supported by the *general guidance* provided by Clark *et al.*

In light of the remarks above, Applicants request that the Examiner withdraw the rejections to the claims under 35 U.S.C. § 103. Reconsideration of the claims is respectfully requested.

Conclusion

Applicants respectfully submit that all the bases for rejection have been overcome by the above remarks. Reconsideration of the application is respectfully requested, and passage of the application to issuance is earnestly solicited.

Respectfully submitted,

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